Remarks

I. Status of the Claims

Claims 104-127 stand rejected by the Office Action dated 16 April 2003. In response, please cancel all pending claims (Claims 104-127) and add new Claim 128.

II. The Specification Provides a Written Description of the Invention of Claim 128 in Compliance with 35 U.S.C. § 112

The Examiner rejected Claim 119 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not contain a written description of the claimed invention. This rejection is obviated, as Claim 119 has been canceled.

The Applicants assert that Claim 128 adds no new matter. Bases for Claim 128 are found throughout the specification, particularly in the following locations in the published PCT application (WO 00/04913):

Table 1. Bases for Claim 128.

	Basis in specification	Actual wording in specification
pharmaceutically acceptable	Page 31, lines 6-13	"the invention provides for stable formulations . . . comprising FSH or FSH variant in a **pharmaceutically acceptable** formulation"
solution formulation	Page 31, lines 6-11	"the invention provides for . . . **solutions** and **formulations**"
comprising human FSH and benzyl alcohol in an aqueous diluent	Page 6, lines 14 through 20	"**comprising FSH . . . and** a preservative selected from the group consisting of . . . **benzyl alcohol . . . in an aqueous diluent**"
	Page 10, lines 7 through 9	"FSH as used herein refers to the FSH produced as a full length mature protein which includes . . . **human** FSH or 'hFSH'"
	Page 65, line 20 through page 66, line 15	See Example 13: samples with 10 mg/mL **benzyl alcohol**

	Basis in specification	Actual wording in specification
concentration of FSH is 5.0 μg/mL to 2 mg/mL	Page 35, lines 8 through 9	"hormone **concentrations** are preferably about **5.0 μg/ml to 2 mg/ml**"
FSH consists of an α-subunit having SEQ ID NO:5 and a ß-subunit having SEQ ID NO:6, held together by noncovalent interactions	Page 3, line 4 through 14	"The members of this family are heterodimers, **held together** generally **by noncovalent interactions** between the two different subunits. The human **FSH** (hFSH) heterodimer **consists of** (i) a mature 92 amino acid **alpha subunit** . . .; **and** (ii) a mature 111 amino acid **beta subunit** that is unique to FSH . . . . The alpha and beta subunits bind non-covalently."
	Page 10, lines 16-19	The protein sequence of the **human FSH alpha subunit** is provided in **SEQ ID NO: 5**, and the protein sequence of the **human FSH beta subunit** is given in **SEQ ID NO:6**.
formulation is suitable for multi-dose administration by injection	Page 9, lines 1 through 2	"are **suitable for** extended or **multiple use**"
	Page 9, lines 10 through 13	"suitable for use in **injectable** . . . systems, e.g., but not limited to, . . . subcutaneous; . . . intramuscular or parenteral . . . liquid formulation"
	Page 7, lines 6 through 7	"invention provides a process for preparing at least one **multi-dose** formulation"

III. Claim 128 Is Not Anticipated Under 35 U.S.C. § 102(a)

The Examiner rejected Claim 104 under 35 U.S.C. § 102(a) as unpatentable over Hirai, *et al.* (U.S. Patent No. 4,659,696; "Hirai"). As Claim 104 has been canceled, the rejection under § 102(a) is obviated.

Claim 128 has been added. Hirai does not anticipate the new claim because Claim 128 is limited to delivery by injection. In contrast, Hirai is directed to "non-injection route" administration. *See* Hirai, abstract ("administered by a . . . non-injection

route"); and col. 1, lines 13-31 ("it is **desired** to develop a dosage form **other than** the **injection**," "the present inventors conducted an intensive study to develop a preparation form for . . . **non-injection administration**," and "drug is used by . . . **non-injection administration**").

Additionally, because Hirai is specifically non-injectable, it does not enable an injectable formulation of the instant invention. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. . . . [A] non-enabled disclosure cannot be anticipatory (because it is not truly prior art) if that disclosure fails to 'enable one of skill in the art to reduce the disclosed invention to practice.'" *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 U.S.P.Q.2d 1385 (Fed. Cir. 2003) (quoting *In re Borst*, 345 F.2d 851, 855, 145 U.S.P.Q. 554, 557 (C.C.P.A. 1962)).

In summary, Claim 128 is novel and thereby patentable over Hirai.

IV. Claim 128 Is Not Obvious Under 35 U.S.C. § 103(a)

A. The Rejections

The Examiner rejected Claims 105-111 and 116-127 (now canceled) under 35 U.S.C. § 103(a) as unpatentable over Hirai in view of Skrabanja, *et al.* (EP 0 853 945 A1; "Skrabanja"). The Applicants assert that new Claim 128 is patentable over the combination of Hirai and Skrabanja.

The Examiner alleged that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Skrabanja regarding concentrations and various forms of FSH and preparations of pharmaceutical compositions and the teachings of Hirai regarding pharmaceutical compositions comprising FSH and benzyl alcohol to make the instant pharmaceutical invention." The Examiner further alleged, "The motivation and expected success is provided by Skrabanja and Hirai. Skrabanja teaches various concentrations of FSH and multi-dose articles of manufacture. Hirai teaches that benzyl alcohol can be used as a preservative."

The Examiner further rejected Claims 112-115 (now canceled) under 35 U.S.C. § 103(a) as unpatentable over Hirai in view of Skrabanja and Boime, *et al.* (U.S. Patent No. 6,238,890; "Boime"). The Applicants assert that new Claim 128 is patentable over the combination of Hirai with Skrabanja and Boime.

The Examiner stated that Boime teaches SEQ ID NO:5 and SEQ ID NO:11. She alleged, "The motivation and expected success is provided by Skrabanja and Boime. Skrabanja teaches that different forms of FSH can be used in the multi-use liquid formulations including analogs, recombinant, modified glycosylated and other forms. Boime teaches that single chain forms are unique starting materials for identifying truncated forms with the activity of the dimers and that using variants of the subunit of FSH will also help identify agonists and antagonist of the glycoprotein hormone activity."

Additionally, in Paper No. 9, the Examiner rejected Claims 92-103 as unpatentable under § 103 over De Meere *et al* (U.S. Patent No. 5,384,132) in view of Buch-Rasmussen *et al.* (U.S. Patent No. 5,945,187) and Bornstein *et al.* (U.S. Patent No. 5,681,822). The Applicants are uncertain whether that rejection was overcome by the claim amendments in Paper No. 13. At any rate, Claims 92-103 has been canceled and any outstanding rejection regarding De Meere with Buch-Rasmussen and Bornstein is obviated. The Applicants assert that new Claim 128 is patentable over the combination of De Meere with Buch-Rasmussen and Bornstein.

As Claims 105-127 have been canceled, all outstanding rejections under § 103(a) are obviated. The evidence and comments below demonstrate that the new claim, Claim 128, is patentable over the cited art.

B. Claim 128 is Not *Prima Facie* Obvious

To establish a prima facie case of obviousness, the Examiner must show: (1) motivation or suggestion to modify or combine the references; (2) reasonable expectation of success; and (3) the combined references must teach all claim limitations. M.P.E.P. § 2143.

The Examiner rejected Claims 105-111 and 116-127 as unpatentable over Hirai (U.S. Patent No. 4,659,696) in view of Skrabanja (EP 0 853 945). New Claim 128 is not obvious over the combination of Hirai and Skrabanja. **Hirai directly teaches that a non-injection route of administration is desirable and can be achieved, teaching away from injection.** ("[A]dministration of a drug by way of injection requires an expert hand and causes pain to the recipient and, for these reasons, **it is desired to develop a dosage form other than the injection.**" Hirai,

col. 1, lines 13-16.) **This provides no motivation to combine Hirai with Skrabanja—a patent specifically directed to Hirai's non-desirable mode of administration!**

Additionally, **Skrabanja does not express or imply any desire to provide a preserved formulation, which Hirai provides**. Skrabanja discloses a sterile aqueous solution of FSH which may be provided in a cartridge containing one or more therapeutic doses. However, neither sterility nor "one or more" doses necessarily suggest the use of a preservative. Sterility refers to the condition of the solution when the cartridge is sealed; it does not indicate the use of an antimicrobial preservative. Skrabanja provides no information on how long the sterile solution can be safely used. More importantly, **Skrabanja does not even hint that a preservative could be used in its solution formulations**.

The skilled artisan would have no motivation to combine Hirai with Skrabanja. Without hindsight reconstruction, no reason can be established for picking and choosing the non-preserved injectable formulation of Skrabanja and combining it with a non-injectable formulation of Hirai. Lacking any motivation to combine Skrabanja with Hirai, the prima facie case is not met, and Claim 128 is not obvious over these references.

The Examiner further rejected Claims 112-115 as unpatentable over Hirai in view of Skrabanja and Boime (U.S. Patent No. 6,238,890). As argued above, Claim 128 is not prima facie obvious over Hirai and Skrabanja. The addition of Boime does not change this. Boime is not helpful to the prima facie case for two reasons. First, all claims to variants have been deleted. Claim 128 only claims human FSH, and Boime does not disclose human FSH. Second, Boime is directed to FSH variants that are covalently bonded to form a single-chain. Covalently bonded FSH subunits are outside the scope of Claim 128. Boime provides no suggestion or motivation to make a preserved non-covalently bonded human FSH formulation. Thus, Claim 128 is not obvious over Hirai in view of Skrabanja and Boime.

Regarding the combination of De Meere (U.S. Patent No. 5,384,132 with Buch-Rasmussen (U.S. Patent No. 5,945,187) and Bornstein (U.S. Patent No. 5,681,822), the Applicants reassert the argument made in Paper No. 12. There is no motivation or suggestion to combine those patents. Lacking such motivation, the

prima facie case of obviousness is not met, and no obviousness rejection using these references can be asserted against Claim 128.

Considering the lack of express or implied motivation to combine any of the cited references, the Applicants assert that no *prima facie* case of obviousness can be established against Claim 128 using the references from the previous rejections.

C. Objective Evidence of the Non-Obviousness of Claim 128

Without conceding in any way that any prima facie case of obviousness could be made against Claim 128, the Applicants reassert the Graham analysis and discussion of objective evidence (provided in Section II of Paper No. 13 and the Declaration of Dr. John M. Beals of Paper No. 14) in support of Claim 128. The Applicants contend that the Beals Declaration is relevant as objective evidence of the non-obviousness of Claim 128. If the Examiner adheres to her statement that other excipients cited by Dr. Beals are preservatives, directly contradicting the factual assertions in the Beals Declaration, the Applicants respectfully invite the Examiner to submit an Examiner's Declaration supporting her assertion. Furthermore, the Applicants request that the Examiner address the specific conclusions of non-obviousness provided in the declaration of Dr. Beals.

V. The Rejections for Nonstatutory Double Patenting Should Be Removed

The Examiner has provisionally rejected Claims 104-127 over copending Application No. 09/973,918 (X-12383P) for nonstatutory double patenting. This provisional rejection is obviated because the copending application has been abandoned. Thus, the Applicants respectfully request that the Examiner remove this provisional rejection.

The Examiner has also provisionally rejected Claims 104-127 over copending Application No. 09/744,431 (X-12383M) nonstatutory double patenting. These claims have been canceled, thereby obviating the provisional rejections. Moreover, because Application No. 09/744,431 and the instant application are commonly owned, the Applicants offer to submit a terminal disclaimer of the instant application to overcome any rejections for double patenting that the Examiner might allege against Claim 128.

VI. Conclusion

The Applicants respectfully assert that all rejections have been obviated by the amendments and remarks herein. The Applicants respectfully remind the Examiner that this application is accelerated under a Petition to Make Special, granted 24 January 2002, and request the Examiner to enter this amendment and advance the application to issue.

Respectfully submitted,

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